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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,006	12/03/2003	Rodney Martin Sambrook	S1011/20168 (case 277A)	7204

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	**PAPER NUMBER**
1618	

NOTIFICATION DATE	DELIVERY MODE
10/22/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)	
	10/728,006	SAMBROOK ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-42,44-50,53-57,59,60 and 62-74* is/are pending in the application.

4a) Of the above claim(s) *46-48,50,66-71 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-42,44,45,49,53-57,59,60,62-65,72 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/362,314.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 7/28/08, in reply to the Office Action mailed 1/28/08, is acknowledged and has been entered. Claims 38-42, 44-50, 53-57, 59, 60, 62-74 are pending, of which claims 46-48, 50, 66-71 and 74 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 38, 53, 55 and 64 have been amended. Claims 38-42, 44, 45, 49, 53-57, 59, 60, 62, 63-65, 72 and 73 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, see page 10 of the Response, with respect to the rejection of claims 64 and 65 under 35 U.S.C. 112, second paragraph, have been fully considered. The rejection has been withdrawn as being overcome by amendment.

Applicant's arguments, see pages 11-13 of the Response, with respect to the rejection of claims 38-42, 44, 45, 53, 54, 59, 60, 62, 63, 72 and 73 under 35 U.S.C. 102(b) as being anticipated by Ishii (JP 04327525) have been fully considered. The rejection has been withdrawn as being overcome by amendment because Ishii does not teach pores comprising a network of coalesced spheres.

Applicant's arguments, see pages 13-16 of the Response, with respect to the rejection of claims 38-42, 44, 45, 53, 54, 59, 60, 62-65, 72 and 73 under 35 U.S.C. 103(a) as being unpatentable over Ishii (JP 04327525) in view of Itokazu have been fully considered. The rejection has been withdrawn as being overcome by amendment because Ishii does not teach pores comprising a network of coalesced spheres.

Applicant's arguments, see pages 16-17 of the Response, with respect to the rejection of claims 38-42, 44, 45, 53-55, 59, 60, 62, 63, 72 and 73 under 35 U.S.C. 103(a) as being unpatentable over Ishii (JP 04327525) in view of Laurencin (US 5,356,630) have been fully considered. The rejection has been withdrawn as being overcome by amendment because Ishii does not teach pores comprising a network of coalesced spheres.

Applicant's arguments, see pages 17-19 of the Response, with respect to the rejection of claims 38-42, 44, 45, 53, 54, 56, 57, 59, 60, 62, 63, 72 and 73 under 35 U.S.C. 103(a) as being unpatentable over Ishii (JP 04327525) in view of Genin (US 6,767,550) have been fully considered. The rejection has been withdrawn as being overcome by amendment because Ishii does not teach pores comprising a network of coalesced spheres.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38-42, 44, 45, 53, 54, 59, 60, 62, 63, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525).

Smith discloses porous ceramic articles. The ceramic is composed of struts, etc. (page 7). The articles are preferably prepared from hydroxyapatite (page 8, line 17). Pore sizes may range from 50 – 150 microns or greater than 150 microns (page 8, lines 6 – 7 and claim 14). The pore sizes in the formed article can be controlled to yield a material with a pre-determined pore size and level of interconnectivity. The porosity may be from 20% to 90% (i.e. a theoretical density of 10 – 80 %) (page 9, line 16). Such an article having a highly microporous structure is produced if sintering is controlled, and has advantages such as it may be filled with drugs such as antibiotics or

growth factors, to act as a slow release agent at the site of an implant. The formed article may be in a variety of shapes (granules, bars, cylinders, etc.) (pages 10, line 18 – page 11, line 5 and claim 15). Regarding the instantly claimed limitation wherein the pores comprise "a network of coalesced spheres," Smith teaches that his ceramic particles are formed by bubbling gas to produce a foam with a large pore structure and a high degree of porosity prepared by introducing bubbles (i.e. spherical) of the correct size and quantity into the suspension or causing smaller bubbles to grow by coalescence (see page 6, lines 9+). See also Figures 1-7 showing essentially spherical pores.

Smith does not specifically recite that the drug located within the pores is present in a degradable support.

Ishii discloses sustained release medicine-containing ceramic porous substances (see TITLE section of English Translation). The sustained release medicine-containing ceramic porous substances are capable of sustaining a medicine for a long period and preventing side effects due to concentrated elution of the medicine by applying a biodegradable substrate containing the medicine, dispersed and held therein to the inner wall surfaces in pores and on the outside surface of a ceramic porous substance (see ABSTRACT section of English Translation). See also Figure 1. The biodegradable substrate containing the medicine is chitin and its derivative or collagen. Calcium phosphate-based ceramics, particularly tricalcium phosphate and hydroxyapatite are especially preferred. The porosity of the ceramic porous substance is preferably 30 – 95 % (i.e. a theoretical density of 5 – 70 %) and the average pore

size is preferably within the range of 10 – 300 μm (see CONSTITUTION section of English Translation). See also working example 1, whereby hydroxyapatite having 90% porosity (i.e. 10% theoretical density) and average pore size of 300 μm is prepared to include collagen and chitin containing kanamycin on the inside surfaces and external surface of the ceramic porous body (paragraph 0006 of the English translation). The base materials which may be used for holding drugs include chitin, chitosan, collagen, etc. (paragraph 0018 of the English Translation). The type of drug which is held includes antibiotics, anticancer drugs, protein drugs, an osteoplasty factor, etc. (paragraph 0019 of English Translation). Regarding claims 42 and 59, the limitations "wherein the pores were formed by sintering a precursor of the carrier under conditions which were below those required for full sintering" or "wherein the second material is introduced into the pores by one or more of centrifugation, immersion, vacuum impregnation or freeze drying" appear to be a product-by-process type limitations. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Regarding claims 72 and 73, wherein the ceramic carrier is shaped for orthopaedic maxillo-facial or cranio-facial replacement, etc. appear to be intended-use

type limitations, because there are no limitations regarding the actual physical shape of the carrier. Ishii teaches his porous ceramic substances to be used as artificial bone (paragraph 0001 of English Translation).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Smith and Ishii and to provide the drug which is infilled in the microporous structure of Smith in a degradable support, such as collagen, chitin, etc. as in Ishii. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because both Smith and Ishii are drawn to release of drugs from a porous hydroxyapatite ceramic (see Smith, pages 10-11; and Ishii, entire document), and because Ishii teaches that such a degradable support provides advantages such as distributed maintenance of drugs and maintaining continuous drug effect over time (see Ishii claim 1, paragraph 0003-0005). Ishii also teaches the advantage of preventing side effects due to concentrated elution of the medicine by applying a biodegradable substrate containing the medicine, dispersed and held therein to the inner wall surfaces in pores and on the outside surface of a ceramic porous substance (abstract).

Claims 38-42, 44, 45, 53, 54, 59, 60, 62-65, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525), further in view of in view of Itokazu (*J. Biomed. Mater. Res.*, 1998, 39, p. 536 – 538).

Smith discloses porous ceramics infilled with drug substances for slow release (page 10, line 18 - page 11, line 3) and Ishii discloses sustained release medicine-containing ceramic porous substances containing a biodegradable substance which contains the medicine dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance, as set forth above. The medicine may be an anticancer drug (paragraph 0019).

Smith and Ishii do not specifically teach that the anticancer drug is MTX.

Itokazu teaches porous apatite ceramics for the local delivery of chemotherapeutic agents. The important issue in treating bone and soft tissue tumors with a chemotherapeutic agent is to maintain local and effective high concentrations of a chemotherapeutic drug with minimum systemic side effects. Localized chemotherapy could reduce the recurrence of bone tumor after curettage and the associated toxicities of chemotherapy. Porous apatite ceramics hydroxyapatite block (HAb) and beta-tricalcium phosphate (TCP) exhibit excellent biocompatibility and have been used as suitable materials for filling bone defects, etc. (page 536, left column). The chemotherapeutic agent MTX was loaded into the pores of the porous apatite ceramics via centrifugation and release profiles were studied (pages 536 – 537). The results showed that MTX released from porous apatite ceramics should be effective in the treatment of metastatic bone tumor, or for minimizing the recurrence of localized benign bone tumors such as giant cell tumors. When used as a strut graft to bone defects and an adjuvant to extended curettage, the MTX-PAC device may provide a means to

reduce recurrence of tumor along and minimize the systemic side effects of chemotherapeutic agents (page 538, left column).

The rejection over Smith in view of Ishii is applied as above. It would have been further obvious to one of ordinary skill in the art at the time of the instant invention to utilize MTX as the drug which was contained within the biodegradable support material (chitin or collagen) in a porous hydroxyapatite ceramic material disclosed by Ishii. One would have been motivated to do so because Ishii teaches that the drug may be an anticancer drug (paragraph 0019) which is used in artificial bone for the therapy of malignant tumor, etc. (paragraph 0001), and because Itokazu teaches that MTX can be successfully released from porous apatite ceramic for the treatment of tumor. One would have had a reasonable expectation of success in doing so because each of Smith, Ishii and Itokazu are concerned with the gradual release of drug via a porous ceramic hydroxyapatite carrier for sustained release and avoidance of systemic side effects (see Smith pages 10-11, Ishii paragraph 0037 and Itokazu page 538).

Claims 38-42, 44, 45, 53-55, 59, 60, 62, 63, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525), further in view of Laurencin (US 5,356,630).

Smith discloses porous ceramics infilled with drug substances for slow release (page 10, line 18 - page 11, line 3) and Ishii discloses sustained release medicine-containing ceramic porous substances containing a biodegradable substance which

contains the medicine dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance, as set forth above.

Ishii teaches collagen or chitin as a biodegradable support for the medicament, rather than PCPP-SA, as claimed.

Laurencin discloses a system for the controlled or sustained release of bioactive substances which interact with local cell populations at a physiological site. The composition is formed of a bioerodible, surface-eroding polymer and the bioactive substance. The “sustained” or "controlled” release of the substance may be either continuous or discontinuous (column 2, lines 20 – 26). Such bioerodible polymers are those which break down or disintegrate over time when placed in contact with biological fluids (column 2, lines 37 – 40). Examples of suitable polymers for such purposes include polyanhydrides such as a co-polymer of PCPP and sebacic acid (PCPP-SA) (column 2, lines 59+). See also claims 1 – 2.

The rejection over Smith in view of Ishii is applied as above. It would have been further obvious to one of ordinary skill in the art at the time of the instant invention to substitute PCPP-SA as a functional equivalent for collagen as the biodegradable support which holds the medicament in the pores of the ceramic substance disclosed by Ishii. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper “functional approach” to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The

key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (collagen and PCPP-SA as biodegradable supports) and their functions (controlled delivery of medicament or bioactive factors) were known in the art at the time of the instant invention. One of ordinary skill in the art could have substituted one known biodegradable support for another, and the results of the substitution would have been predictable, that is controlled or sustained release of a medicament upon biodegradation of the support material.

Claims 38-42, 44, 45, 53, 54, 56, 57, 59, 60, 62, 63, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525), further in view of Genin (US 6,767,550).

Smith discloses porous ceramics infilled with drug substances for slow release (page 10, line 18 - page 11, line 3) and Ishii discloses sustained release medicine-containing ceramic porous substances containing a biodegradable substance which contains the medicine, including anticancer agents, dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance, as set forth above.

Smith and Ishii do not specifically teach that the pores contain layers of medicament and degradable support, each layer being different from its neighbors, or alternating medicament-free and medicament-containing layers.

Genin discloses hydroxyapatite based bioresorbable materials incorporated with anti-cancer agents to form an implant used for treatment against cancer. Sustained release of the anti-cancer agents may be achieved after implantation at the targeted sites. The dosage of the anticancer agent, the microstructure, morphology, and composition of the bioresorbable material allow control of the release profile (abstract). The material may be a layered sustained release biocompatible implants comprising a first layer consisting of hydroxyapatite, and a second layer consisting of hydroxyapatite, a bioresorbable material, and doxorubicin. The first layer may further comprise polymers, collagen, etc. The first and second layers of the implant may be porous or dense. The implant is introduced within bone tissue adjacent to, around, or inside a tumor (see claims 1 – 9).

The rejection over Smith in view of Ishii is applied as above. It would have been further obvious to one having ordinary skill in the art at the time of the instant invention to provide the biodegradable support material which holds a medicament in the pores of the ceramic substance disclosed by Ishii in the form of alternating layers. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because each of Smith, Ishii and Genin are directed to the sustained release of a medicament from a hydroxyapatite-based implant for the treatment of bone tumor, and because Genin discloses that such multilayered structures are useful in implants for which the resorption rate is designed, or can provide benefits such as periodical release of anti-cancer agents (see claims 1 – 9; column 4, lines 11 – 15; column 6, lines 19 – 21).

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS